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RAPID COMMUNICATION

Wnt genes in colonic polyposis predisposition

To the Editor,

Much of the genetic predisposition to polyposis, and particularly to serrated polyposis (SP), remains unknown. Only germline pathogenic variants in *RNF43*, a tumor suppressor that exerts negative feedback in the Wnt/β-catenin signaling pathway, have been causally linked to some SP cases (<2%), a disease associated with increased risk of colorectal cancer (CRC).[1] Most known hereditary CRC and polyposis genes affect DNA repair, BMP/TGF-β, or Wnt signaling, being the latter associated with adenomatous and serrated polyposis phenotypes.[2] Based on this observation, we evaluated the presence and role of germline variants in those pathways in unsolved polyposis patients.

Exome sequencing data from 44 SP patients were analyzed considering genes involved in DNA repair (311 genes), BMP/TGF-β (102 genes), and Wnt signaling pathways (301 genes). Pathway- and gene-centered burden tests were performed to evaluate their association with SP. Details on patients, controls, genes, and methodological approaches are described in Supplementary Material and Methods, and Tables S1–3. The study was approved by the Ethics Committees of IDIBELL (PR073/12, MedPerCan_PR156/17) and University Hospital Dr. Trueta (POLSER v.2_09/03/2017), and informed consent was obtained from all subjects. Additional and/or detailed results and discussion complementing this article are shown in Supplementary Material.

Pathway-based burden tests showed no overall association of SP with germline damaging or predicted damaging variants in BMP/TGF-β or DNA repair genes, not even when considering specific DNA repair pathways (Table S4). However, variants in known hereditary cancer genes affecting those two pathways were identified, including pathogenic variants in *BRCA1*, *BRCA2*, or *BRIP1*, and variants of unknown significance in *MLH1*, *PMS2*, or *BMPR1A* (Table S5). Nevertheless, gene-centered burden tests for these genes did not show an association with SP (Tables S6 and S7). Although relevant for the clinical management of carrier probands and relatives, a causal relationship with the SP phenotypes is highly unlikely, since the well-described associated phenotypes do not include SP. Re-evaluation of the polyps in the *BMPR1A* carrier would be advisable to identify potential features suggestive of a juvenile histology.

Germline (predicted) damaging variants in DNA repair or TGF-β pathway genes previously proposed as candidate CRC or SP predisposing genes were identified (Supplementary Bibliography), including variants in *ATR*, *ERCC6*, *TP53BP1*, *WRN*, and *XPC* (DNA repair), and *RBL1* (BMP/TGF-β) (Table S5). Gene burden tests identified statistically significant associations with SP for *XPC* and *WRN*, but not for the other candidate genes (Tables S6 and S7). In particular, *XPC* c.2404G>A; p.(Gly802Ser), *XPC* c.2647dup; p.(Ser883Phefs*3), *WRN* c.2273+1G>T and *WRN* c.2300C>G; p.(Thr767Arg), were detected in our SP patients.

For Wnt signaling genes, significant enrichment of damaging and predicted damaging alleles was observed in SP patients (44/88; 50%) compared to controls (43,514/118,190; 37%) ($p = 0.01$) (Table S4). This association was not detected in nonpolyposis CRC patients (Supplementary Results; analysis of 1,006 familial/early-onset CRC patients not selected for polyposis). *RNF43* c.394C>T; p.(Arg132*) was identified in one patient.[3] Germline predicted pathogenic variants were identified in several genes previously proposed as CRC predisposing genes (Supplementary Bibliography), including *LRP6* c.2690A>G; p.(Asn897Ser) or *SMARCA4* c.3830C>T; p.(Pro1277Leu), as well as a variant of unknown significance in *APC*: c.8445G>T; p.(Lys2815Asn) (Table S5).

Gene-centered burden analyses considering the Wnt genes that harbored damaging and predicted damaging variants in the 44 SP patients (Table S8), showed statistically significant associations with SP for 11 individual genes: *CCDC88C*, *DKK1*, *DKK4*, *HECW1*, *ITPR3*, *PSMB3*, *PSMC3*, *PSME4*, *RNF43*, *TLE4*, and *WNT9B* (Fig. S1 and Table 1).

The identified 10 new candidate genes for SP predisposition (all but *RNF43*) were analyzed in 98 additional unsolved SP patients and 101 unsolved adenomatous polyposis (AP) patients, taking into consideration that germline pathogenic variants in main components of the Wnt

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Table 1 Gene-based burden analysis for the 10 potential SP predisposing genes identified in this study. Numbers in bold indicate statistically significant results.

Gene	Cohort or study	Disruptive alleles (frameshift, stop-gain, start-loss, and canonical splice-site)		Disruptive and [b]predicted pathogenic missense (REVEL $\geq$0.35)	
		n/total alleles (%)	OR (95%CI); *p* value	*n*/total alleles (%)	OR (95%CI); *p* value
CCDC88C	[a]Controls	29/118,190 (0.03%)		242/118,190 (0.20%)	
	SP	0/88 (0.00%)	0.00 (0.00—185.42); $p = 1$	2/88 (2.27%)	**11.33 (1.34—42.64); $p = 0.01$**
	Validation-SP	0/196 (0.00%)	0.00 (0.00—82.61); $p = 1$	0/196 (0.00%)	0.00 (0.00—9.33); $p = 1$
	Validation-AP	0/202 (0.00%)	0.00 (0.00—79.83); $p = 1$	1/202 (0.50%)	2.42 (0.06—13.79); $p = 0.34$
	Meta-analysis				
	TOTAL SP	0/284 (0.00%)	0.00 (0.00—56.78); $p = 1$	2/284 (0.70%)	3.46 (0.41—12.74); $p = 0.12$
	TOTAL Polyposis	0/486 (0.00%)	0.00 (0.00—33.09); $p = 1$	3/486 (0.62%)	3.03 (0.62—9.00); $p = 0.08$
DKK1	Controls	3/118,190 (0.003%)		32/118,190 (0.03%)	
	SP	0/88 (0.00%)	0.00 (0.00—3588.05); $p = 1$	1/88 (1.14%)	**42.43 (1.03—258.14); $p = 0.02$**
	Validation-SP	0/196 (0.00%)	0.00 (0.00—1472.26); $p = 1$	0/196 (0.00%)	0.00 (0.00—74.25); $p = 1$
	Validation-AP	0/202 (0.00%)	0.00 (0.00—1422.08); $p = 1$	1/202 (0.50%)	18.37 (0.45—110.67); $p = 0.06$
	Meta-analysis				
	TOTAL SP	0/284 (0.00%)	0.00 (0.00—1025.04); $p = 1$	1/284 (0.35%)	13.04 (0.32—78.52); $p = 0.08$
	TOTAL Polyposis	0/486 (0.00%)	0.00 (0.00—588.28); $p = 1$	2/486 (0.41%)	**15.26 (1.77—59.98); $p = 0.01$**
DKK4	Controls	18/118,190 (0.02%)		96/118,190 (0.08%)	
	SP	1/88 (1.14%)	**75.43 (1.79—493.23); $p = 0.01$**	1/88 (1.14%)	14.14 (0.35—82.74); $p = 0.07$
	Validation-SP	0/196 (0.00%)	0.00 (0.00—138.52); $p = 1$	0/196 (0.00%)	0.00 (0.00—23.82); $p = 1$
	Validation-AP	1/202 (0.50%)	**32.63 (0.79—209.90); $p = 0.03$**	1/202 (0.50%)	6.12 (0.15—35.29); $p = 0.15$
	Meta-analysis				
	TOTAL SP	1/284 (0.35%)	**23.20 (0.55—147.44); $p = 0.04$**	1/284 (0.35%)	4.35 (0.11—25.00); $p = 0.21$
	TOTAL Polyposis	2/486 (0.41%)	**27.14 (3.04—113.90); $p = 0.003$**	2/486 (0.41%)	5.08 (0.61—18.96); $p = 0.06$
HECW1	Controls	13/118,190 (0.01%)		334/118, 190 (0.28%)	
	SP	1/88 (1.14%)	**104.47 (2.43—699.69); $p = 0.01$**	1/88 (1.14%)	4.06 (0.10—23.36); $p = 0.22$
	Validation-SP	0/196 (0.00%)	0.00 (0.00—199.07); $p = 1$	0/196 (0.00%)	0.00 (0.00—6.74); $p = 1$
	Validation-AP	3/202 (1.49%)	**136.96 (24.83—498.50); $p = 2.7 \times 10^{-6}$**	3/202 (1.49%)	**5.32 (1.08—15.90); $p = 0.02$**
	Meta-analysis				
	TOTAL SP	1/284 (0.35%)	**32.11 (0.75—213.88); $p = 0.03$**	1/284 (0.35%)	1.25 (0.03—7.05); $p = 0.55$
	TOTAL Polyposis	4/486 (0.82%)	**75.43 (17.85—244.99); $p = 6.3 \times 10^{-7}$**	4/486 (0.82%)	**2.93 (0.79—7.62); $p = 0.05$**
ITPR3	Controls	117/118,190 (0.10%)		1709/118,190 (1.45%)	
	SP	0/88 (0.00%)	0.00 (0.00—43.86); $p = 1$	5/88 (5.68%)	**4.11 (1.30—9.99); $p = 0.01$**
	Validation-SP	0/196 (0.00%)	0.00 (0.00—19.48); $p = 1$	4/196 (2.04%)	1.42 (0.38—3.70); $p = 0.37$
	Validation-AP	5/202 (2.48%)	**25.62 (8.07—62.46); $p = 2.4 \times 10^{-6}$**	19/202 (9.41%)	**7.08 (4.15—11.41); $p = 2.0 \times 10^{-10}$**
	Meta-analysis				
	TOTAL SP	0/284 (0.00%)	0.00 (0.00—13.40); $p = 1$	9/284 (3.17%)	**2.23 (1.01—4.31); $p = 0.02$**
	TOTAL Polyposis	5/486 (1.03%)	**10.49 (3.33—25.37); $p = 0.0002$**	28/486 (5.76%)	**4.17 (2.73—6.13); $p = 1.4 \times 10^{-9}$**
PSMB3	Controls	0/118,190 (0.00%)		61/118, 190 (0.05%)	
	SP	0/88 (0.00%)	—	1/88 (1.14%)	**22.25 (0.55—132.11); $p = 0.05$**
	Validation-SP	0/196 (0.00%)	—	0/196 (0.00%)	0.00 (0.00—37.92); $p = 1$
	Validation-AP	0/202 (0.00%)	—	0/202 (0.00%)	0.00 (0.00—36.81); $p = 1$

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	Meta-analysis				
	TOTAL SP	0/284 (0.00%)	–	1/284 (0.35%)	6.84 (0.17–39.90); $p = 0.14$
	TOTAL Polyposis	0/486 (0.00%)	–	1/486 (0.21%)	3.99 (0.10–23.21); $p = 0.23$
PSMC3	Controls	8/118,190 (0.01%)		64/118, 190 (0.05%)	
	SP	0/88 (0.00%)	0.00 (0.00–778.31); $p = 1$	1/88 (1.14%)	**21.21 (0.52–125.13); $p = 0.05$**
	Validation-SP	0/196 (0.00%)	0.00 (0.00–354.24); $p = 1$	0/196 (0.00%)	0.00 (0.00–36.08); $p = 1$
	Validation-AP	0/202 (0.00%)	0.00 (0.00–343.65); $p = 1$	2/202 (0.99%)	**18.46 (2.17–70.36); $p = 0.01$**
	Meta-analysis				
	TOTAL SP	0/284 (0.00%)	0.00 (0.00–244.40); $p = 1$	1/284 (0.35%)	6.52 (0.16–37.95); $p = 0.15$
	TOTAL Polyposis	0/486 (0.00%)	0.00 (0.00–142.96); $p = 1$	3/486 (0.62%)	**11.46 (2.30–35.24); $p = 0.003$**
PSME4	Controls	16/118,190 (0.01%)		250/118,190 (0.21%)	
	SP	0/88 (0.00%)	0.00 (0.00–350.68); $p = 1$	2/88 (2.27%)	**10.97 (1.3–41.27); $p = 0.02$**
	Validation-SP	0/196 (0.00%)	0.00 (0.00–157.54); $p = 1$	0/196 (0.00%)	0.00 (0.00–9.03); $p = 1$
	Validation-AP	1/202 (0.50%)	**36.74 (0.87–238.52); $p = 0.03$**	4/202 (1.98%)	**9.53 (2.55–25.09); $p = 0.001$**
	Meta-analysis				
	TOTAL SP	0/284 (0.00%)	0.00 (0.00–10.63); $p = 1$	2/284 (0.70%)	0.00 (0.00–6.21); $p = 1$
	TOTAL Polyposis	1/486 (0.21%)	15.23 (0.36–98.41); $p = 0.07$	6/486 (1.23%)	**5.90 (2.13–13.11); $p = 0.0007$**
TLE4	Controls	0/118,190 (0.00%)		60/118,190 (0.05%)	
	SP	0/88 (0.00%)	–	1/88 (1.14%)	**22.63 (0.56–134.21); $p = 0.04$**
	Validation-SP	0/196 (0.00%)	–	1/196 (0.51%)	10.10 (0.25–59.07); $p = 0.10$
	Validation-AP	0/202 (0.00%)	–	0/202 (0.00%)	0.00 (0.00–37.41); $p = 1$
	Meta-analysis				
	TOTAL SP	0/284 (0.00%)	–	2/284 (0.70%)	**13.97 (1.65–53.11); $p = 0.01$**
	TOTAL Polyposis	0/486 (0.00%)	–	2/486 (0.41%)	**8.13 (0.96–30.85); $p = 0.03$**
WNT9B	Controls	3/118,190 (0.003%)		333/118,190 (0.28%)	
	SP	0/88 (0.00%)	0.00 (0.00–3588.05); $p = 1$	2/88 (2.27%)	**8.23 (0.98–30.88); $p = 0.03$**
	Validation-SP	0/196 (0.00%)	0.00 (0.00–1472.26); $p = 1$	1/196 (0.51%)	1.82 (0.05–10.30); $p = 0.43$
	Validation-AP	3/202 (1.49%)	**589.98 (78.97–3818.75); $p = 9.7 \times 10^{-8}$**	7/202 (3.47%)	**12.70 (5.00–26.96); $p = 2.3 \times 10^{-6}$**
	Meta-analysis				
	TOTAL SP	0/284 (0.00%)	0.00 (0.00–1025.04); $p = 1$	3/284 (1.06%)	**3.78 (0.77–11.25); $p = 0.05$**
	TOTAL Polyposis	3/486 (0.62%)	**244.35 (32.66–1857.82); $p = 1.3 \times 10^{-6}$**	10/486 (2.06%)	**7.44 (3.51–13.97); $p = 2.0 \times 10^{-6}$**

a: Controls correspond to the 59,095 non-Finnish European, non-cancer individuals from the gnomAD v.2.1.1 dataset (exomes and genomes). b: A REVEL score $\geq$0.35 was considered for pathogenicity prediction. Prediction scores were obtained from the Ensembl Variant Effect Predictor (VEP).

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canonical signaling pathway (*APC*, *AXIN2*) also predispose to AP. The data analyzed were obtained through the SOLVE-RD ERN GENTURIS consortium. The identified variants are listed in Table S9. Gene-based burden tests for the 10 new candidate SP predisposing genes combining the original and validation SP cohorts (meta-analysis) confirmed a significant association with SP for *DKK4*, *HECW1*, *ITPR3*, and *TLE4* (borderline non-significant for *DKK1* and *WNT9B;* $0.05< p \leq 0.08$). Association with AP was detected for *DKK4*, *HECW1*, *ITPR3*, *PSMC3*, *PSME4*, and *WNT9B* (borderline non-significant for *DKK1*). When considering all 247 polyposis (SP and AP) patients (494 alleles), the association with the disease was detected for all genes except for *CCDC88C* and *PSMB3* (Table 1).

Polyposis genes involved in Wnt signaling, *i.e. APC*, *AXIN2*, and *RNF43*, are Wnt-negative regulators. The wild-type forms of these genes' products ultimately allow the degradation of β-catenin in the cytoplasm, avoiding its translocation to the nucleus and subsequent activation of genes involved in cancer initiation and progression[4] (Fig. S2). We hypothesized that all or most newly identified Wnt-related polyposis genes are also Wnt-negative regulators. By using a TOP/FOP dual luciferase assay that measures TCF transcriptional activity,[3] we detected a significant inhibitory effect on Wnt signaling for *DKK1*, *DKK4*, *HECW1*, *TLE4*, and *WNT9B* (Fig. S3). *PSMC3* and *PSME4*, components of the proteasome, did not show an effect on Wnt signaling inhibition. *ITPR3*, which belongs to the Wnt/Ca^{2+} (β-catenin-independent) signaling, was not tested.

All damaging (truncating) variants and at least one missense variant per gene were functionally evaluated using the optimized assay (Fig. S3). Truncating variants in *DKK1* and *DKK4* showed significant reversion of the inhibitory effect on Wnt signaling. Although non-significant, reversion or partial reversion of the Wnt inhibitory effect was also observed for truncating mutations in *HECW1* and *TLE4*.

A statistically significant functional effect was observed for *DKK1* p.(Arg236His) and *DKK4* p.(Gly38Alafs*49). Not reaching statistical significance, reversion or partial reversion of the Wnt inhibitory effect was observed for *HECW1* p.(Glu541*) ($p = 0.099$ *vs.* wildtype) and *TLE4* p.(Arg546Cys) ($p = 0.0875$). A neutral effect (evidence against pathogenicity) was detected for *DKK1* p.(Cys127Phe), *DKK4* p.(Ile221*) (full protein: 223 amino acids), *WNT9B* p.(Cys89*), *WNT9B* p.(Arg97Leu), and *WNT9B* p.(Gln345*). Inconclusive results were obtained for *HECW1* p.(Leu1058Serfs*28) and *WNT9B* p.(Arg94Gln) (Fig. S3).

Our findings suggest an association of some Wnt-related genes with SP predisposition, but also, for some of them, with AP. According to our results, there may be a predominance of SP for *DKK1*, *DKK4*, and *TLE4*, and of AP phenotypes for *PSMC3* and *PSME4*, while the association with both types of polyposis was observed for *HECW1*, *ITPR3*, and *WNT9B*. The small number of variants identified precluded the analysis of phenotypes (polyp types and cancer risks) associated with each gene. Identification of additional carriers will help better define gene-specific phenotypes.

The strengths of our study include the analysis of different polyposis cohorts/datasets and the use of a variant prioritization strategy and burden tests focused on the analysis of genes affecting relevant pathways for polyposis and CRC predisposition. The main limitation, based on the low prevalence of (predicted) pathogenic variants in patients, is the limited sample sizes, which limit the statistical power of the tests, together with the analysis of only European cohorts. Supported by the functional evidence obtained for the genes and variants, we reported as significant any association with p-value ≤ 0.05, despite not being adjusted for multiple comparisons. Another issue was the use of a relatively lax cutoff for pathogenicity prediction of missense variants (REVEL ≥ 0.35). Gene-burden tests considering a REVEL score >0.5 for missense variants maintained, with slight modifications, the association with polyposis predisposition (Table S10).

In conclusion, our findings suggest that Wnt-activating variants in *DKK1*, *DKK4*, *HECW1*, *TLE4*, and *RNF43* predispose to serrated polyposis, and, at least in the case of *HECW1*, also to adenomatous polyposis. An association with polyposis predisposition was also identified for *ITPR3*, *PSMC3*, *PSME4*, and *WNT9B*.

Author contributions

IQ contributed in a highly relevant manner to the conceptualization and design of the work, data curation, formal analysis, investigation, methodology, validation, visualization, and writing of the original draft. MT and PM contributed to the formal analysis of data, investigation, and methodology, and reviewed and edited the manuscript. IBAWtP contributed to the formal analysis, validation, manuscript review and editing, and provided resources. SP, IS, VS-L, MN, VP, JB, AS, YvH, and GAstuti contributed to the validations and provided resources. DT, MP, RR, RT, GP, DP, and SB contributed to the bioinformatic analysis of data. CM, NG-A, and GAiza contributed to different parts of the investigation. EH-F, NH, RMdV, RdV, and SA provided resources, contributed to the validation study, reviewed and edited the manuscript, and supervised students. GC contributed to the funding acquisition, resources, and reviewed and edited the manuscript. LV designed and conceptualized the study, and administered and supervised the project and the team, wrote the original draft, and contributed in a very relevant manner to the formal analysis, methodology, and interpretation of data.

Conflict of interests

The authors declare that they have no conflict of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2022.12.002.

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